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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,626	11/26/2003	Daniel Pratt	19043-501	9707

30623 7590 08/26/2010

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
08/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,626	PRATT ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-31, 39-41, 44-50, and 52-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *46 and 55-67* is/are allowed.

6)☒ Claim(s) *22-30,40-45,47-50 and 52-54* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 22-31, 39-41, 44-50, and 52-67 are pending. Applicants previously cancelled claim 1-3, 4-21, 32-38 and 51. Claims 42-43 are newly cancelled. Claims 55-67 are new. Receipt and consideration of Applicants' amended claim set and remarks/arguments submitted on June 9, 2010 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments. Applicants' claim amendments have necessitated new grounds of rejection set forth below.

Specification

The disclosure is objected to because of the following informalities: on page 10, line 30 and page 11, line 1, specific gravity is indicated as having units of gm/ml, which is incorrect, because by definition specific gravity is a unitless quantity (see claim objection below).

Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 22 is objected to because of the following informalities: the units of measurement listed for specific gravity should be removed, because specific gravity is unitless (i.e. specific gravity = ([density of a liquid in units of g/mL]/[density of water in units of g/mL]). Thus, the

units cancel and specific gravity is a unitless quantity). It is also noted that the unit for grams is not "gm," as recited in claim 22, but rather "g." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-30, 40-45, 47-50, and 52-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

An analysis based upon the most relevant Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence

of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth/Description of Claims

Applicants' claims are broad with regards to the therapeutic agent, polymer, and buoyancy agent. Applicants' claimed method requires that the administered compositions are buoyant in the cerebrospinal fluid (CSF).

Nature of the invention/State of the Prior Art/Guidance/Working Examples

Applicants' claimed method is a method of intrathecally delivering a composition comprising biodegradable polymer particles containing therein a therapeutic agent and a buoyancy agent, such that the composition is controllably buoyant in the cerebrospinal fluid (CSF). Applicants' specification from page 10, line 30 through page 11, line 2, indicates that the specific gravity of CSF ranges from about 1.0063 mg/mL [sic] to 1.0075 gm/ml [sic]. Buoyancy is understood to mean the ability of something to float in a particular liquid medium. The tenth edition of Merriam Webster's Collegiate Dictionary defines buoyancy on page 152 to mean:

"1a. the tendency of a body to float or to rise when submerged in a fluid; 1b. the tendency of a liquid to exert an upward force on a body placed in it…"

Thus, the claimed method recites something that is impossible: that the composition is buoyant in the CSF, because the specific gravity of the composition is recited in the claimed method as being equivalent to the typical specific gravity of CSF. Simple logic leads the ordinary skilled artisan to conclude that something that does not have a lower specific gravity than the CSF will not float and will not be buoyant. It is noted that Applicants' specification supports this position,

because at page 10, lines 27-30, Applicants distinguish between compositions exhibiting what Applicants denote as being "negative buoyant" (i.e. compositions having a specific gravity greater than that of CSF), "neutrally buoyant" (i.e. compositions having a specific gravity equal to that of CSF), or "positively buoyant" (i.e. compositions having a specific gravity lower than that of CSF). Because Applicants' claimed method only refers to the compositions being buoyant, it is a reasonable interpretation that these compositions must be able to float. Compositions having the same specific gravity as the CSF will not be buoyant (i.e. will not float), but rather will mix with the CSF. Because the compositions recited in amended claim 22 are required to have the same specific gravity as that of the CSF, it is impossible for these compositions to be buoyant. Applicants' specification provides no guidance or working examples on how to prepare or make compositions having the same specific gravity as the CSF float (i.e. be buoyant). In conclusion, the claimed method, as recited in claim 22 and claims dependent therefrom, is not enabled because it is impossible for a composition administered intrathecally into the CSF, which has the same specific gravity as the CSF, to be buoyant.

Response to Arguments

Applicant's arguments with respect to claims 22-31, 39-41, 44-45, 47-50, and 52-54 have been considered but are moot in view of the new ground(s) of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-31, 39-41, 44-45, 47-50, and 52-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is confusing, because it recites that the composition ***comprises*** a specific gravity having a value from 1.0063 gm/ml [sic] to 1.0075 gm/ml [sic]. This is confusing, because the word "comprising" denotes a constituent part of the composition; however, a property, such as specific gravity, is not a part of any composition, but rather an inherent characteristic of a composition. Thus, it is nonsensical to state that a composition comprises a specific gravity. However, it is noted that compositions may "have, "possess," or "exhibit" properties, such as specific gravity.

Claim 22 is also confusing, because it recites that the administered composition is controllably buoyant in the cerebrospinal fluid (i.e. the composition is buoyant in the CSF and necessarily floats in the CSF). The word "buoyant" means that something floats in a particular liquid. In Applicants' specification from page 10, line 30 through page 11, line 2, Applicants indicate that the specific gravity of CSF ranges from about 1.0063 mg/mL [sic] to 1.0075 gm/ml [sic]. Thus, the specific gravity range recited in claim 22, if construed as being a property exhibited by the administered composition, is the same as that of the typical specific gravity of the CSF. As a result, the administered composition will not float in the CSF (i.e. it will not be buoyant), rendering the claim internally inconsistent.

The remaining claims are rejected as depending from a rejected claim.

Response to Arguments

Applicant's arguments with respect to claims 22-31, 39-41, 44-45, 47-50, and 52-54 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-30, 40-45, 47-50, and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. (U.S. Patent No. 5,560,933) ("Soon-Shiong") in view

of Harris, D.C. ("Quantitative Chemical Analysis, 4th ed., W. H. Freeman and Co.: 1995, pp 26).

Applicant Claims

Applicants claim (1) a method of administering a therapeutic agent within the central nervous system (CNS) comprising intrathecal administration of a composition to a subject's CNS, wherein said composition comprises a biodegradable polymer having a therapeutic agent and a buoyancy agent contained therein, wherein the buoyancy agent is selected from gases and oils and is controllably buoyant within the CSF, and the composition *comprises* a specific gravity from 1.0063 gm/ml [sic] to 1.0075 gm/ml [sic].

As noted above, it is unclear what is meant by a composition "comprising a specific gravity ranging from 1.0063 to 1.0075." It is also noted that Applicants have indicated on page 11, lines 1-2 that the ordinary skilled artisan would recognized the CSF specific gravity may vary in magnitude between individuals.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Soon-Shiong teaches methods for in-vivo delivery (e.g. intrathecal administration) of substantially water insoluble pharmacologically active agents (e.g. taxol) and compositions useful thereof (title; abstract; col. 3, lines 24-29; and col. 4, lines 28-33). Soon-Shiong's invented compositions comprise particles of substantially water insoluble active agents contained within a shell having a cross-sectional diameter of no greater than 10 microns, wherein a cross-sectional diameter of less than 1 micron is most preferred (col. 5, lines 23-30). Suitable active

agents for incorporation into Soon-Shiong's invented compositions include **aspirin, ibuprofen, estrogen (i.e. a hormone), prednisolone, cortisone, hydrocortisone, anesthetics, immunosuppressive agents**, and preferably **taxol (i.e. a cytotoxic agent)** (col. 5, lines 31-56). The invented composition may also contain nutritional agents within the shell, such as **amino acids**, sugars, **proteins, carbohydrates, fat-soluble vitamins, such as vitamins A,D, E, and K**, and combinations thereof (col. 5, line 65 through col. 6, line 3). **Amino acids, sugars, proteins, carbohydrates, and vitamins A, E, and K read on active agents that are "other plant products".** The shell of Soon-Shiong's invented particles can be made of any natural or synthetic biocompatible polymer that may be cross-linked via the formation of disulfide linkages, such as **proteins** (e.g. **albumin, insulin, hemoglobin, immunoglobulins, fibronectin, fibrinogen**, etc.**), oligopeptides, polysaccharides** (e.g. starch, cellulose, chitin, dextrans, etc.), and synthetic polymers, which are amenable to chemical functionalization to introduce sulfhydryl moieties, such as polyvinyl alcohol, **polyhydroxyethyl methacrylate**, polyacrylic acid, polyacrylamide, polyvinyl pyrrolidone, etc.

Soon-Shiong teaches that optionally in the preparation of the compositions dispersing agents in which the active agent is dissolved or suspended may also be included, such as **vegetable oils (e.g. soybean oil, coconut oil, olive oil safflower oil, cotton seed oil, and the like**), aliphatic, cycloaliphatic, or aromatic hydrocarbons having 4-30 carbon atoms, aliphatic or aromatic alcohols, esters, ethers, and alkyl or aryl halides, all having 2-30 carbon atoms are indicated as being suitable dispersing agents (col. 6, lines 47 through col. 7, line 4). The invented particles with a biocompatible shell and an active agent contained therein are typically **delivered as a suspension in a biocompatible aqueous liquid** (col. 7, lines 15-22). In the

preparation of Soon-Shiong's invented compositions, it is contemplated that **the particle shells contain therein both the substantially water insoluble active agent dissolved or suspended in the dispersing agent** (col. 8, line 65 through col. 9, line 7). In Example 2 (col. 11, lines 12-35), Soon-Shiong teaches **an albumin protein shell containing soybean oil**. Shells comprising **a mixture of albumin and PEG-thiol** with a molecular weight of 2,000 g/mol are also exemplified in Example 11, col. 16, lines 20-55). The inclusion of PEG is art-recognized as increasing protein/enzyme in vivo circulation time and is expected to prolong drug release in vivo (col. 9, lines 38)

Kim teaches the **administration of therapeutic agents to the CSF to treat neurological disorder**s by administration of **dispersion systems having a higher specific gravity than the CSF** (i.e. hyperbaric compositions), such as compositions comprising encapsulated iohexol, iodixanol, metrzamide, carbohydrates, etc. as well as **hypobaric dispersion systems (i.e. having a lower specific gravity than the CSF)** (title; abstract; claims 1 and 31-37).

Harris teaches that the **density of air at 25 °C and 1 atm of pressure is 0.012 g/ml**. Therefore, the specific gravity of air at 25 °C and 1 atm of pressure is approximately 0.012. Air is a mixture of nitrogen, oxygen, and other gases.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Soon-Shiong does not exemplify a method of administering a therapeutic agent by intrathecal administration. This method, however, is suggested per the teachings of Soon-Shiong. Soon-Shiong does not explicitly teach the inclusion of buoyancy agents. This deficiency is nonetheless obvious per Soon-Shiong's teachings and is also explicitly taught by Kim. Soon-

Shiong does not teach a buoyancy agent that is a gas or a mixture of oxygen and nitrogen (e.g. air). This deficiency is cured by the combined teachings of Kim and Harris.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to utilize the invented particles to administer an active pharmaceutical agent intrathecally, because Soon-Shiong explicitly teaches that the invented compositions are suitable for the in vivo administration of active substances and defines in vivo delivery to include intrathecal administration. Soon-Shiong does not explicitly teach the inclusion of buoyancy agents, however, Soon-Shiong's invented particles may comprise a dispersing agent, such as vegetable oils, which Applicants' admit are suitable buoyancy agents. Thus, Soon-Shiong's teachings suggest the administration of biocompatible aqueous suspensions of particles comprising (i) a biocompatible shell, such as cross-linked albumin, which is also biodegradable, and (ii) an active agent dissolved or suspended in a dispersing agent, such as soybean oil, which is necessarily a buoyancy agent, as admitted by Applicants. Regarding the actual specific gravity of Soon-Shiong's exemplified/suggested particulate compositions, Applicants are reminded that the Office lacks laboratory facilities to test the prior art compositions to ascertain their specific gravities. Thus, the burden is properly shifted to Applicants to demonstrate that Soon-Shiong's compositions do not have or exhibit a specific gravity value within a specified range. An ordinary skilled artisan would have been motivated to administer Soon-Shiong's compositions intrathecally and would have had a reasonable expectation of success in intrathecally

administering these compositions, because Soon-Shiong's compositions are taught as being suitable for intrathecal administration. Regarding the intrathecal administration of Soon-Shiong's compositions to patients diagnosed with a central nervous system disorder, the preferred active agent in Soon-Shiong's compositions is a taxol, which is a well-known anticancer agent.

It would have been prima facie obvious to include a buoyancy agent in Soon-Shiong's compositions, because Kim teaches the incorporation of materials having a specific gravity higher (i.e. hyperbaric) or lower (i.e. hypobaric into the dispersions systems to affect targeted delivery within the CSF. It is noted that Applicants have admitted on pages 10-11 that the specific gravity of the CSF may vary from one individual to another. Therefore, what may be a hyperbaric composition in one individual, may be hypo- or isobaric in another individual, and Kim's teachings do not teach away from compositions having a particular specific gravity value. An ordinary skilled artisan would have been motivated to combine the teachings of Soon-Shiong and Kim, because both references teach the intrathecal administration of active agents. Regarding the identification of materials that have a lower specific gravity (i.e. hypobaric materials), Kim does not explicitly identify these materials, but common sense would lead the ordinary skilled artisan to consider air, because air is a gas, and gases are less dense and necessarily have a lower specific gravity than water and the CSF. For example, air, which is well known to be a mixture of nitrogen, oxygen, and other gases, is known to have a density of 0.012 g/ml. Thus, air would have a specific gravity of less than 1.0063 (i.e. 0.012) and it would have been prima facie to include air within Soon-Shiong's dispersion systems as modified by the teachings of Kim to obtain a dispersion system that is hypobaric (i.e. has a specific gravity value

lower than the specific gravity of the CSF). An ordinary skilled artisan would have had a reasonable expectation of modifying Soon-Shiong's teachings per the teachings and suggestions of Kim, because it was known to include materials to adjust the specific gravity of dispersion systems relative to the specific gravity of the CSF (Kim).

Furthermore, regarding the recited specific gravity ranges, Applicants have identified vegetable oils as having a specific gravity that is less than 1.0063. Regarding the incorporation of PEG (polyethylene glycol), it would have been prima facie obvious to include PEG. Regarding claims 51-52, because Soon-Shiong teaches that the particles may contain fat-soluble vitamins as the active ingredient (e.g. Vitamin E), most of these vitamins are oils, and that the dispersing agent may be removed, Soon-Shiong's teachings impliedly suggest biodegradable particles containing oil that would act as both a buoyancy agent and a therapeutic agent when administered to the CSF (e.g. vitamin E). Thus, it is reasonable to conclude that Soon-Shiong's compositions comprising particles containing therein vitamin E as a therapeutic agent and dispersing agent would necessarily have a specific gravity within the range recited in Applicants' claims.

Regarding the active agents, it is noted that "cancer" reads on a central nervous system disorder, as evidenced by Applicants' claim 28. Anti-cancer agents, such as taxol, read on the term "neuroprotective agent" as defined by Applicants in paragraph [0024] (i.e. "neuroprotective agent" refers to drugs which alleviate a symptom of or prevent damage to the brain or spinal cord"), because an anti-cancer agent would prevent further damage to the brain or spinal cord caused by cancer as well as treat symptoms caused by the cancer. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 6/9/2010 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that the rejection is improper, because none of the cited references explicitly teach a particular range of specific gravity for the compositions administered.

This argument is unpersuasive, because, as noted above, Soon-Shiong, the primary reference, teaches intrathecal administration and fairly suggests compositions comprising biodegradable polymer particles (e.g. albumin particles) containing therein vitamin E, soybean oil, etc. and Applicants' claims indicate that the administered compositions comprise biodegradable polymer particles containing a therapeutic agent and a buoyancy agent, such as an oil, gas, or combination thereof. Because the teachings of the prior art references fairly suggest the intrathecal administration of compositions comprising the same composition components recited in Applicants' claims, it is proper to conclude that the compositions suggested by the prior art necessarily exhibit the same or overlapping specific gravity values. Applicants are reminded that the Office lacks laboratory facilities to test the prior art compositions to ascertain their specific gravities. Thus, the burden is properly shifted to Applicants to demonstrate that Soon-Shiong's compositions do not have or exhibit a specific gravity value within the recited range. Regarding Kim's teachings, it is noted that the specific gravity value of the CSF varies between individuals. As a result, compositions that may have a higher specific gravity than the

CSF specific gravity in one individual, will likely have a specific gravity that is the same or lower than the CSF specific gravity in a different individual. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 31 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. (U.S. Patent No. 5,560,933) ("Soon-Shiong") in view of Kim et al. (WO 94/26250) (New IDS reference) and Harris, D.C. ("Quantitative Chemical Analysis, 4th ed., W. H. Freeman and Co.: 1995, pp 26), as applied to claims 22-30, 40-45, 47-50, and 52-54 above, and further in view of Russell et al. (*Bone Marrow Transplantation*, 1999, *24*, pp 1177-1183) (already of record) and Vook et al. (US 2003/0129233).

Applicant Claims

Applicants claim method as described above, wherein the biodegradable polymer is poly(lactide-co-glycolide) (PLGA) and in some embodiments the active agent consists of living cells selected from bone marrow cells (e.g. red blood cells), fetal neural cells, or stem cells.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Soon-Shiong have been set forth above in the instant office action and are herein incorporated by reference. The teachings of Russell were set forth in the office action mailed 6/2/06 and are restated herein. Russell is provided herein to demonstrate that living cells,

specifically bone marrow stem cells and blood cell stem cells, are art recognized therapeutic agents used in the treatment of leukemia. Leukemia is a kind of cancer and living cells are clearly substantially water insoluble active agents.

Russell teaches comparative studies of the treatment of patients with acute myelogenous leukemia (AML) and Myelodysplasia (MDS) who received sibling transplants **with stem cells** from peripheral blood (blood cell transplant, BCT) or bone marrow (BMT). Russell concluded by stating that while disease-free survival may be better using BCT than BMT for AML, it may greatly impair quality of life, due to a higher proportion of acute graft-versus-host disease (GVHD) (abstract).

Vook teaches particularly effective compositions for the localized delivery of chemotherapeutic hydrophobic anticancer agents, inclusive of **paclitaxel (taxol)**, doxorubicin, 5-fluorouracil, campthothecin, cisplatin, and metronidazole, their corresponding derivatives and functionally equivalents, and combinations thereof from **PLGA microspheres** [0006]. Vook's invented PLGA/Taxol microspheres afford controlled/sustained release of taxol and offer many clinical advantages, such as (1) improved patient compliance, as the number of drug dosings are decreased because the depot contains an amount of drug equivalent to multiple doses; (2) isolation depot from the tissue via its incorporation in PLGA thus reducing the drug concentration exposed to the one time and decreasing the chance of tissue injury of the drug copolymer, tissue at any at the depot site; (3) controlled drug release, which may allow for increased dosages of hydrophobic drugs to be administered without systemic toxicity complications. In terms of specific clinical applications of this technology, hydrophobic

drug/PLGA formulations are envisioned to play a role in the treatment regiment of cancer and of infection [0287].

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Soon-Shiong lacks the teaching of an intrathecal administration method, wherein the active agent consists of living cells. This deficiency is cured by the teachings of Russell. Soon-Shiong lacks the teaching of an intrathecal administration method, wherein the biodegradable polymer is PLGA. This deficiency is cured by the teachings of Vook.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Soon-Shiong to substitute taxol for bone marrow stem cells or red blood stem cells, because both bone marrow stem cells or red blood stem cells have been shown as being suitable for treating leukemia a kind of cancer and taxol is a known anti-cancer agent. Furthermore, it would have been prima facie obvious to substitute taxol for bone marrow stem cells or red blood stem cells to treat leukemia, a kind of cancer, because both taxol and bone marrow stem cells or red blood stem cells are known to be suitable for the treatment of cancer. An ordinary skilled artisan would have been motivated to utilize bone marrow stem cells or red blood stem cells as the active agent in Soon-Shiong's invented compositions, because bone marrow stem cells or red blood stem cells are clearly substantially water insoluble active agents. An ordinary skilled artisan would have had a reasonable expectation of success upon incorporation of bone marrow stem cells or red blood

stem cells into Soon-Shiong's invented compositions, because bone marrow stem cells or red blood stem cells are substantially water insoluble active agents. Regarding the use of PLGA as the biodegradable polymer shell, this would have been prima facie obvious, because PLGA is a well-known conventional biocompatible and biodegradable polymer. An ordinary skilled artisan would have been motivated to modify Soon-Shiong's teachings and utilize PLGA/taxol microspheres, because PLGA/taxol microspheres are conventional compositions used to deliver taxol, are reasonable expected to enhance patient compliance due to the controlled/sustained release properties of the PLGA/taxol microspheres, and taxol is isolated from the body in the PLGA microsphere and, thus, less likely to induce tissue damage. An ordinary skilled artisan would have had a reasonable expectation of modifying Soon-Shiong's teachings to utilize PLGA as the polymer shell and obtain suspensions wherein the polymer shells contained taxol suspended in a dispersing agent (e.g. vegetable oil) and deliver the resulting composition intrathecally, because Soon-Shiong's compositions are suitable for intrathecal administration and taxol/PLGA are well known compositions. Thus, an ordinary skilled artisan would have been motivated to utilize Soon-Shiong's invented composition modified to contain bone marrow or red blood stem cells in to treat cancer via intrathecal administration with a reasonable expectation of success.

Response to Arguments

Applicant's arguments filed 6/9/2010 have been fully considered but they are not persuasive. Applicants arguments do not specifically address the merits of the instant rejection, but are understood to be the same as those arguments presented to traverse the first rejection

made under § 103(a) above. The Office's rebuttal arguments are herein incorporated by reference and the rejection is maintained.

Allowable Subject Matter

Claims 46 and 55-67 are allowed. The prior art does not teach or fairly suggest the preparation and administration of therapeutic compositions comprising biodegradable polymer particles containing therein a therapeutic agent in combination with a hydrofluorocarbon.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The online article, entitled, "Density of Cooking Oil" is relevant because it establishes the typical specific gravity values of various common cooking oils, such as coconut, corn, cotton seed, olive, peanut oil, etc ("Density of Cooking Oil" accessed on August 19, 2010 at hypertextbook.com/facts/2000/IngaDorfman.shtml). Misra et al. ("Incorporation of vitamin E in poly(3hydroyxbutyrate)/Bioglass composite films: effect on surface properties and cell attachment," *J.R. Soc. Interface*, **2009**, *vol. 6*, pp 401-409) is not prior art, but is relevant because it establishes that the density of vitamin E is 0.950 g/ml and by inference that the specific gravity of vitamin E is 0.950 (see section 2.2 on page 402).

Claims 22-30, 40-45, 47-50, and 52-54 are rejected. Claim 22 and the specification are objected. Claims 46 and 55-67 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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